REMARKS

Reconsideration is requested.

Claims 12-33 are pending. Claims 24-33 have been added, and claims amended, as presented in the Amendment of August 8, 2003 in the parent application Serial No. 09/795,289. Support for the claims may be found throughout the specification. No new matter has been added.

A further copy of the noted priority document will be provided under separate cover as a courtesy to the Examiner once received by the undersigned.

The Section 112, first paragraph "enablement", rejection of claims 17-19 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The specification, taken with the advanced level of skill in the present art, adequately describes how to make and use the claimed invention. The specification is directed to one of ordinary skill in the art.

The successful use of HCV envelope proteins or portions thereof as medicaments is known in the art. The applicants believe that U.S. Patent No. 6,635,257, and specifically Examples 4-6 of same, provide evidence of the advanced level of skill in the art. Moreover, U.S. Patent No. 7,101,561, and specifically Examples 15-18 of same, and U.S. Patent Application Publication No. 2004-0126395 A1, and specifically, for example, Examples 19-21 of same, further evidence the advanced level of skill in the art.

Further, the applicants submit that the applicants' assignee is currently performing a clinical phase IIb trial wherein humans are immunized with sulfonated E1,

aiming at reducing fibrosis, demonstrating that one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation. The Examiner is further requested to see, for example, Example 23 and Fig. 52 of the assignee's U.S. Patent No. 7,048,930, wherein antibodies in mice were induced by HCV viral-like particles (VLPs) formed of sulphonated E1 compared to VLPs formed of alkylated E1.

The applicants again submit that there is ample evidence and teaching for one of ordinary skill in the art to make and use HCV envelope proteins as an immunogenic composition to produce an immune response which is more likely than not to be beneficial in ameliorating infection or treating disease.

As for the Examiner's statement that sulphonation can be toxic to the animal that is being immunized (see page 4 of the Office Action dated January 22, 2007), the Examiner has not provided any evidence in support of the assertion. Rather, the applicants submit that the use of sulphonated proteins is known in the art (although not in vaccination) such that any issue or concern of toxicity has been resolved and there is thus no reason to believe that the same would require undue experimentation to overcome with HCV envelope proteins.

Specifically, sulphonated proteins, and especially, immunoglobulins (IgG) have already been used in man. The reversible nature of sulphonation and restoration of functionality was shown after intravenous injection. In addition no safety related problems were published even after high dose and long term use.

Sulphonated IgG have been injected in small numbers of patients in the early 70s and no side effects have been observed after intravenous injection of high doses (100

mg/ kg) for periods up to 11 years (See Vox Sang. 1979;37(1):14-20[1] and Biotherapy. 1993-94;7(2):101-7[2]). Studies with sulphonated IgG have demonstrated the restoration of the disulphide bridges in the IgG and all IgG effector functions were regained (See Vox Sang. 1979;37(1):14-20, Vox Sang. 1983;45(2):144-54[3] and Vox Sang. 1983;45(2):155-65[4]). This signifies that the product is *in vivo* desulphonated and that

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[1] Clinical effect and metabolism of S-sulfonated immunoglobulin in 7 patients with congenital humoral immunodeficiency. Yamanaka T, Abo W, Chiba S, Nakao T, Masuho Y, Tomibe K, Noguchi T.

7 patients with primary humoral immunodeficiency were given an S-sulfonated IgG preparation, 100 mg/kg i.v. at intervals of 3--4 weeks, for treatment of, or prophylaxis against, infection. The clinical effects and metabolism of S-sulfonated IgG were studied. No side reactions attributable to S-sulfonated IgG occurred in any of the patients. The S-sulfonated IgG was completely transformed into intact IgG within 24 h after administration, and had a mean half-life of 21 days, comparable to that of intact IgG. Complete restoration of IgG Fc fragment activity occurred within 24 h following injection, as assessed by reversed passive cutaneous anaphylaxis.

[2] Long-term follow up of patients with common variable immunodeficiency treated with intravenous immunoglobulin: reevaluation of intravenous immunoglobulin replacement therapy. IVIG therapy in CVID. Mushiake K, Motoyoshi F, Kondo N, Shimizu H, Orii T.

Five patients with common variable immunodeficiency treated in our hospital between December 1979 and December 1990 were given six kinds of intravenous immunoglobulin preparations (pepsin treated, S-sulfonated, polyethylene glycol treated, pH4 treated, alkylated, and pH4.25 formulation preparation) for replacement therapy. Duration of the therapy ranged from 7.6 to 11 years. Incidences of fever and acute infections were variable among patients, but no significant differences were seen in the incidences among periods given each preparation. Three cases revealed abnormal pulmonary functions in tests. Adverse reactions were rarely seen in our study periods, and no severe reactions were observed. No significant differences were seen in incidences of adverse reactions. Postinfusion levels of serum complement slightly decreased from preinfusion levels. However, the decrease in complement was not related to any adverse reaction. No long-term complications such as transmission of hepatitis have been observed. Our data suggest that no obvious differences exist between the efficacy and safety of each IVIG preparation. Differences of efficacy of IVIG replacement therapy may be due to the variable pathophysiology of each patient.

[3] S-sulfonation: a reversible chemical modification of human immunoglobulins permitting intravenous application. I. Physicochemical and binding properties of S-sulfonated and reconstituted IgG. Gronski P, Hofstaetter T, Kanzy EJ, Luben G, Seiler FR.

S-sulfonation represents a reversible chemical modification of disulfide bonds by which under the special conditions chosen only about 2.2 cystine units per IgG molecule are cleaved. Physicochemical and functional evidence for reconstitution is presented. Molecules reconstituted in vitro or in vivo regain, within a few hours, a reactivity (antigen binding, immunoprecipitation, Clq-mediated cross-linking of immune complexes) comparable to equimolar control preparations.

[4] S-sulfonation: a reversible chemical modification of human immunoglobulins permitting intravenous application. II. Effect on Fc-mediated effector functions. Hofstaetter T, Gronski P, Kanzy EJ, Schorlemmer HU, Seiler FR.

The generation and release of mediators of inflammation and anaphylaxis via activation of complement or of Fc receptor-bearing cells is held responsible for adverse reactions observed upon intravenous administration of standard immunoglobulins. They are caused by immunoglobulin G (IgG)

the original 'S-S' bridges are reformed. This demonstrates that sulphonation is a reversible reaction and that the sulfon group is removed, probably by the competition with other protein thiols or small thiol compounds in serum (gluthation, cysteine).

The claims are submitted to be supported by an enabling disclosure and withdrawal of the Section 112, first paragraph "enablement", rejection of claims 17-19 is requested.

The Section 102 rejection of claims 16, 17, 20 and 22 over Grakoui (Journal of Virology (1993), Vol. 67, pp 1385-1395), is traversed. The Section 102 rejection of claims 16, 17, 20 and 22 over Watanabe (U.S. Patent No. 5,610,009), is traversed. Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing comments.

Initially, the applicants submit that the Section 112, first paragraph "written description", rejection of claims 12-22 is contrary to the above-noted Section 102 rejections as, if the claims are described in the art then the specification need not describe the claimed invention as a specification need not re-teach that which is (allegedly) known in the art. The Examiner is requested to be consistent in rejecting the claims and to withdrawal either the written description rejection or to withdrawal the Section 102 rejections.

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effector functions predominantly located in the Fc region of the molecule and 'activated' by aggregate formation. Their functional activity depends on the correct conformation of the C gamma 2 domains of Fc and are therefore impaired or even abrogated by S-sulfonation of the hinge disulfide bonds, as demonstrated in this communication: S-sulfonated IgG (S-IgG) has no anticomplementary activity and does not interact with Fc-receptors anymore. After antigen binding, i.e. immune complex (IC) formation, sulfonated IgG is about half as potent as standard IgG in complement activation or phagocyte stimulation (human monocytes and granulocytes). The two activities synergize, however, so that in the presence of complement S-IgG IC are as effective phagocyte activators as standard IC. Moreover, S-sulfonation being the only chemical modification of immunoglobulins that is reversible, it can be demonstrated that all IgG effector functions important for antigen removal are regained by reconstitution of the disulfide bonds.

The applicants believe that the cited art do not teach or suggest an isolated HCV envelope protein of the claims.

Grakoui et al. are understood to disclose bacterial expression constructs harboring a part of the HCV E1 protein - in particular amino acids 236-382 - or a part of the HCV E2 protein - in particular amino acids 393-670 (see Table 1, p. 1386). These expression products are prepared by SDS-polyacrylamide gel electrophoresis and are only used for obtaining HCV-specific polyclonal antisera suitable for immunoprecipitation of SDS-denatured HCV antigens (p. 1386, right-hand column). Watanabe et al. disclose mammalian expression systems for expressing HCV (truncated) E1 proteins (see Fig. 2) that are used for diagnostic and therapeutic purposes.

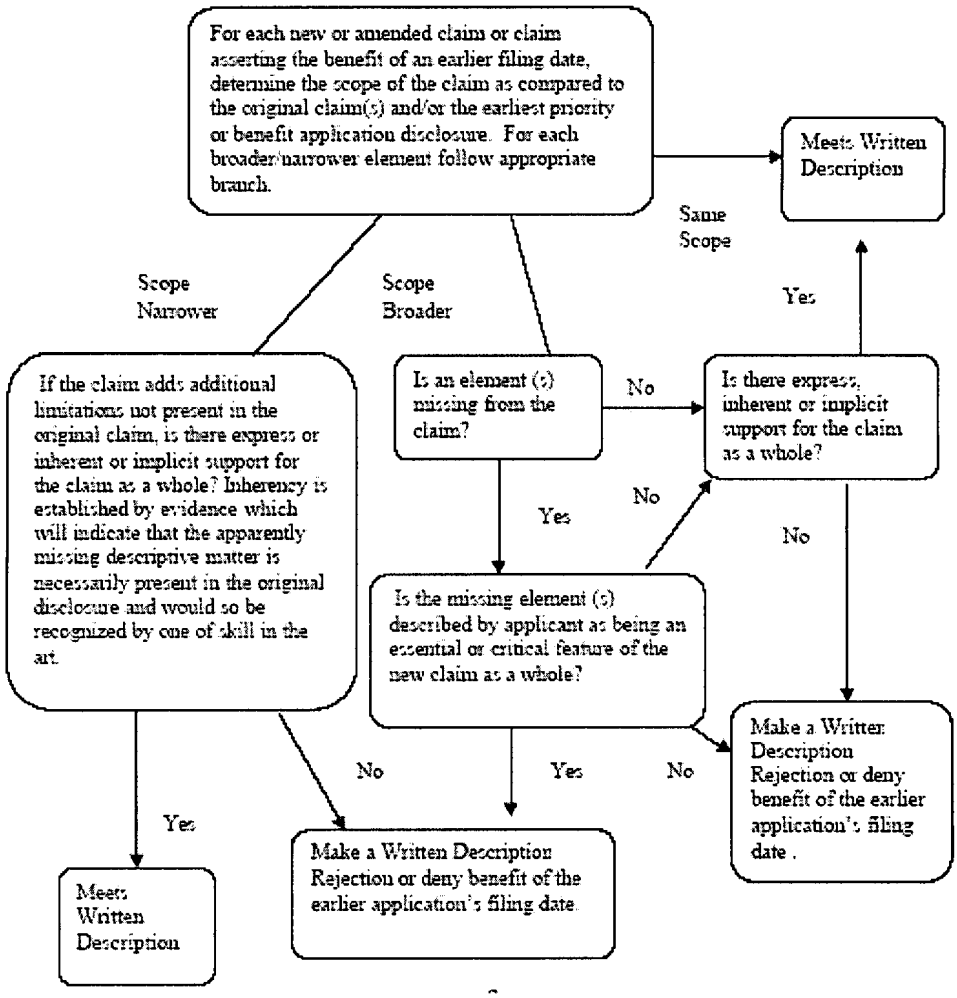
Both Grakoui et al. and Watanabe et al. fail to teach the isolation of the HCV envelope proteins. The applicants believe that one of ordinary skill in the art will appreciate that purified HCV proteins as used in the present application and invention relate to isolated HCV proteins in essentially pure form. According to the present invention, an "isolated" HCV protein relates to an HCV protein composition that is at least 35% pure (see also the description on page 12-13 of the application WO 01/30815). The isolated HCV proteins are not disclosed in Grakoui et al. nor in Watanabe et al.

Withdrawal of the Section 102 rejections is requested.

The Section 112, first paragraph "written description", rejection of claims 12-22 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner has identified a passage of the specification which describes the aspect of the claims which is the basis of the "written description" rejection. The claims have been amended to be consistent with the passage of the specification cited by the Examiner. Specifically, the "parts" of the recited proteins have been further defined as functionally equivalent parts. The applicants further note that the originally-filed claims also included the presently recited description of the claimed parts.

The applicants note in this regard that the USPTO "Revised Interim Written Description Guidelines Training Materials" available on the USPTO website (http://www.uspto.gov/web/offices/pac/writtendesc.pdf), provide the following "Decision Tree" for determining whether the claims of an application are supported by an adequate written description:



The first step of this "decision Tree" involves determining the scope of the claims as compared to the original claims. As the original claims include the "parts" element as presently claimed, the applicants believe the claims are supported by an adequate written description and withdrawal of the Section 112, first paragraph "written description", rejection is requested.

The applicants further note, for completeness, that at the time of the priority date of the present invention, a variety of constructs for expression of HCV envelope proteins and fragments thereof were available (see, for example, U.S. Patent No. 6,150,134). In

the present invention, a different purification procedure has been fully described (see Example 2, 5 and 6) to arrive at purified native-like HCV envelope proteins, comprising a Cys residue with a reversible redox status. The differences in purification method are clearly outlined as compared to purification of irreversibly protected HCV envelope proteins (as in U.S. Patent No. 6,150,134). The applicants believe that the present specification will lead one of ordinary skill in the art to conclude that the applicants were in possession of the claimed invention at the time the application was filed and that no further experimental evidence would be required in the specification for a representative number of fragments covered by the genus of the claims. The specification describes "functional equivalent part thereof" as "a part or a fragment of said HCV [envelope] protein that contains in its amino acid sequence at least one cysteine, the redox status of which is variable..." as recognized by the Examiner and the specification provides the methods for producing said HCV envelope proteins.

The claims are supported by an adequate written description and withdrawal of the Section 112, first paragraph "written description", rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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